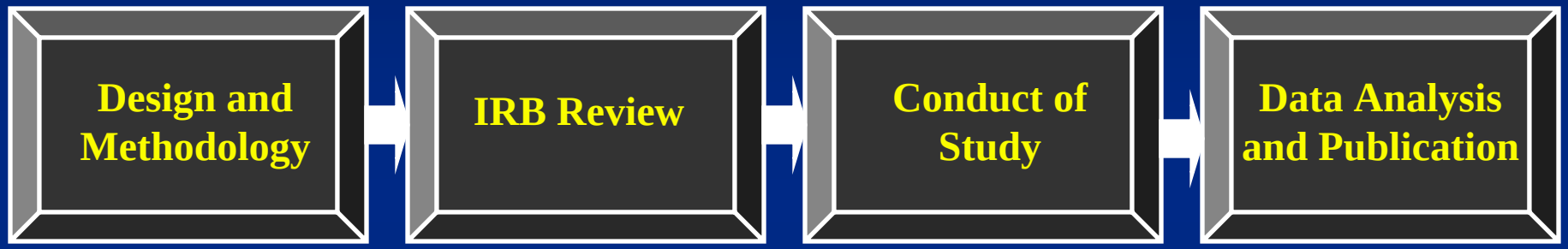
Research Involving Persons at Risk for Impaired Decisionmaking

Donald L. Rosenstein, M.D.
National Institutes of Health

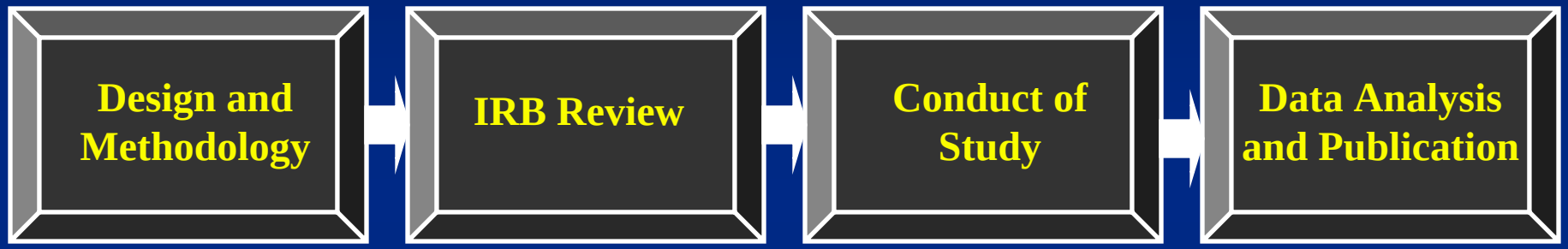
Scope

- **Non-emergency research with adults**
- **Overlapping domains**
  - competence
  - cognitive impairment and decisionmaking capacity
  - ability to provide informed consent
  - vulnerability
- **Dimensional phenomena and categorical decisions**
- **IRB-oriented perspective; focus on process**

Research with Decisionally Impaired Subjects



Research with Decisionally Impaired Subjects



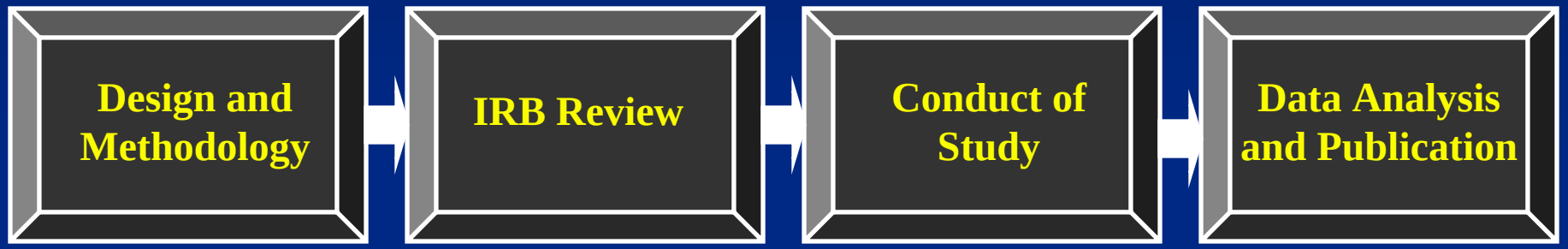
Central Ethical Tension: *Medical Progress vs. Exploitation*

Research with Decisionally Impaired Subjects

Design and Methodology → **IRB Review** → **Conduct of Study** → **Data Analysis and Publication**

Central Ethical Tension: *Medical Progress vs. Exploitation*

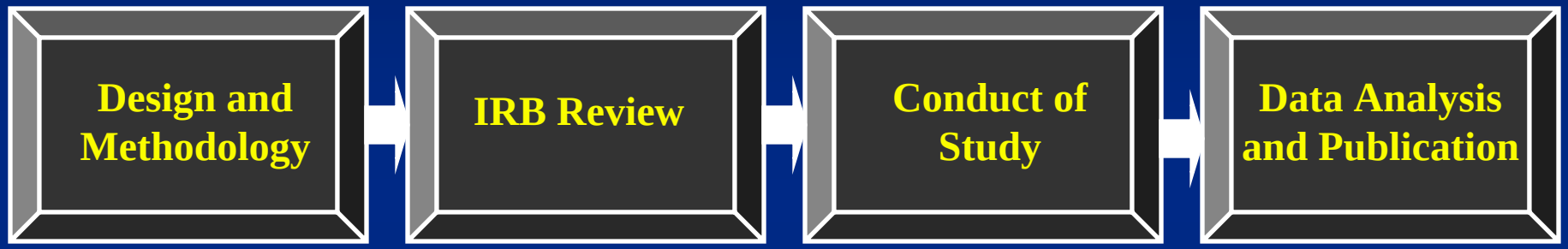
Research with Decisionally Impaired Subjects



Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

Research with Decisionally Impaired Subjects



Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

(OHRP, FDA, NBAC, MAS 87-4, Advocacy Groups, etc)

45 CFR 46.111
Criteria for IRB Approval of Research

(b) When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

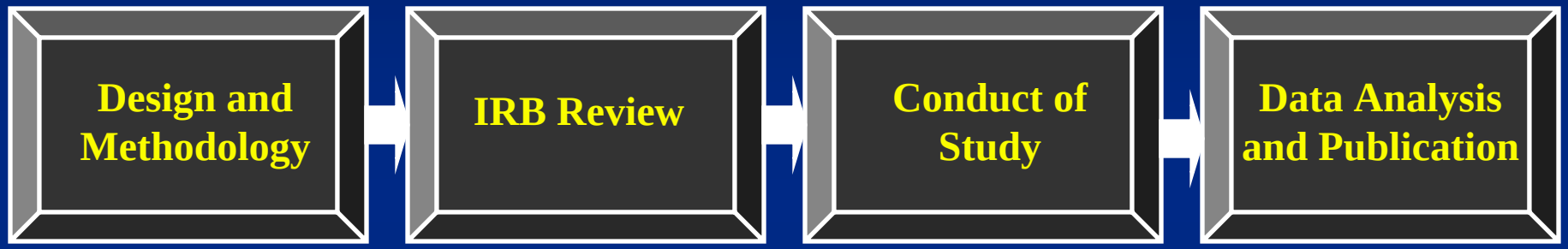
Central Questions

1. Who is vulnerable because of a mental disability?

2. What are the appropriate additional safeguards for vulnerable subjects?

3. How can these safeguards be optimally implemented ?

Research with Decisionally Impaired Subjects



Central Ethical Tension: *Medical Progress vs. Exploitation*

Regulations, Laws, Policies and Public Opinion

Conceptual Models and Empirical Data

Design and Methodology

- Subject population
  - Subjects unable to provide informed consent
  - Early stage and at-risk subjects
- Nature of study (medication free, CNS active drug)

Research With Impaired or Potentially Impaired Subjects

- Medication trial for Alzheimer's Disease
- ECT trial for delusional depression
- Placebo-controlled study in acute mania
- MRS study of a delirium model
- Establishing cell lines for genetics studies of mental retardation
- Tryptophan depletion in autism (adults)
- Medication-free studies of schizophrenia

The Most Contentious Case

Research

with subjects who

can not provide informed consent

that offers

no prospect of direct medical benefit

and involves

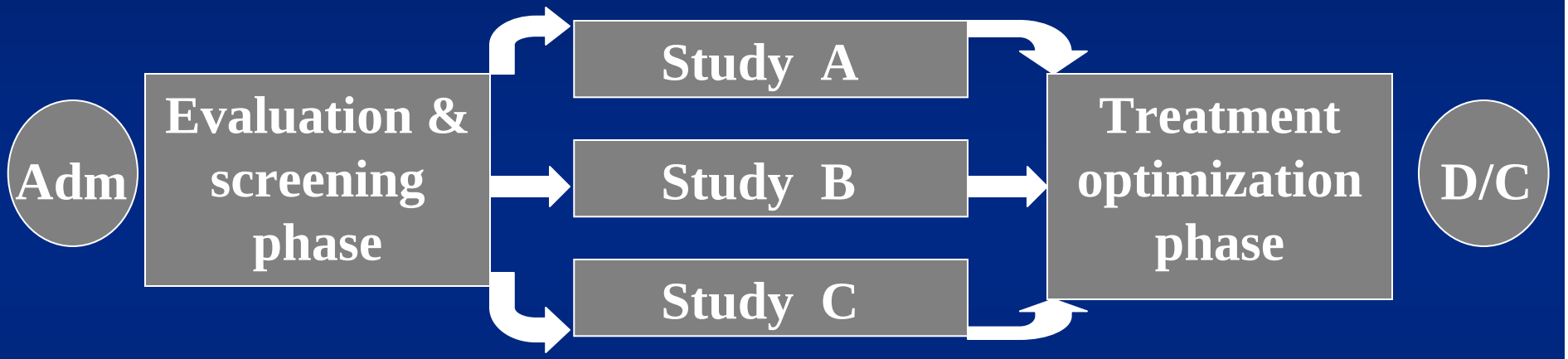
more than minimal risk

Design and Methodology

- Subject population
  - Subjects unable to provide informed consent
  - Early stage and at-risk subjects
- Nature of study (medication free, CNS active drug)
- Scientific review
  - value
  - “necessity clause”
  - feasibility
- Study outcomes

IRB Review

Clinical Care in the Context of Clinical Research



clinical Rx	study meds	clinical Rx
data collection (e.g. ratings, scans)		

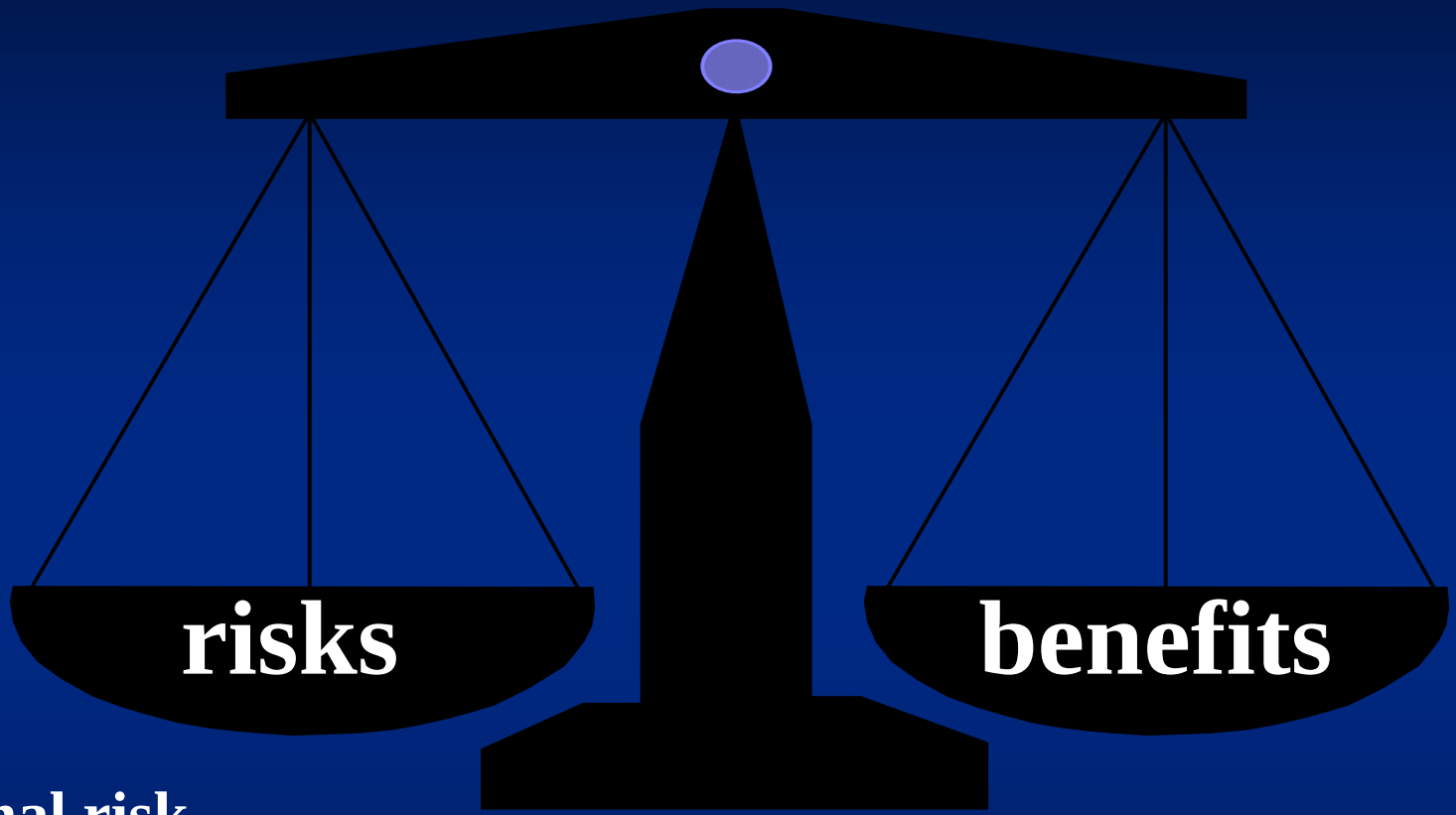
IRB Review

- Can the scientific question be answered with capacitated subjects?
  - Analogy to pediatric research
  - Exceptions
    - Prospect of benefit
    - Prior commitment from subject
    - Minimal risk?

IRB Review

- **Can the scientific question be answered with capacitated subjects?**
- **What are the relevant risks and benefits?**

Institutional Review Board



- minimal risk
- minor increment over minimal risk (children)
- greater than minimal risk

- direct benefit to the subject
- benefit to society
- (indirect benefits to subject)

IRB Review

- Can the scientific question be answered with capacitated subjects?
- What are the relevant risks and benefits?
- What is the nature of the anticipated decisionmaking impairment?

Factors Influencing Decisionmaking Capacity

- Memory, attention, concentration
- Conceptual organization
- Psychosis and hallucinations
- “Executive” function

Factors Influencing Decisionmaking Capacity

- Memory, attention, concentration
- Conceptual organization
- Psychosis and hallucinations
- "Executive" function
- Risk assessment
- Mood
- Intuition
- Insight
- Behavior
- Duty and altruism
- "Relatedness"

Will Subjects Be Able to Provide Informed Consent?

- Subjects **who are currently** unable to provide informed consent
- Subjects **who will become** unable to provide informed consent
- Subjects **who are at increased risk** of becoming unable to provide informed consent

IRB Review

- Can the scientific question be answered with capacitated subjects?
- What are the relevant risks and benefits?
- What is the nature of the anticipated decisionmaking impairment?
- Are adequate safeguards in place?

Conduct of Study

- Recruitment
- Capacity/consent assessment

Triggers for Capacity Assessment

- Concern about a class of prospective subjects
  - Protocol designed to enroll “at-risk” subjects
  - Protocol that may precipitate loss of decisional capacity

Triggers for Capacity Assessment

- Concern about a class of prospective subjects
  - Protocol designed to enroll “at-risk” subjects
  - Protocol that may precipitate loss of decisional capacity
- Concern about an individual
  - Prior to or at the time of enrollment
  - During study participation

Assessment of Decisionmaking Capacity (DMC)

- Presumption of capacity/competence
- Medical aspects of assessment of DMC
  - Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania

Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Capacity to Give Informed Consent for Research

Does this individual have a medical, neurological or psychiatric disorder that compromises his or her capacity to understand, appreciate and reason with respect to the details of a given study?

Clinical judgment

Can this person give informed consent and should they be enrolled into the study?

Ethical judgment

Assessment of Decisionmaking Capacity (DMC)

- Presumption of capacity/competence
- Medical aspects of assessment of DMC
  - Dehydration, medication toxicity, sickness, delirium, psychosis, severe depression, grief, mania
- Who does this?
- How is it done?

MacArthur Competence Assessment Tool (MacCAT-CR)

UNDERSTANDING

purpose of study; what tests and procedures

major risks, discomforts and possible benefits

APPRECIATION

is the main purpose to benefit you?

differences between this study and regular care

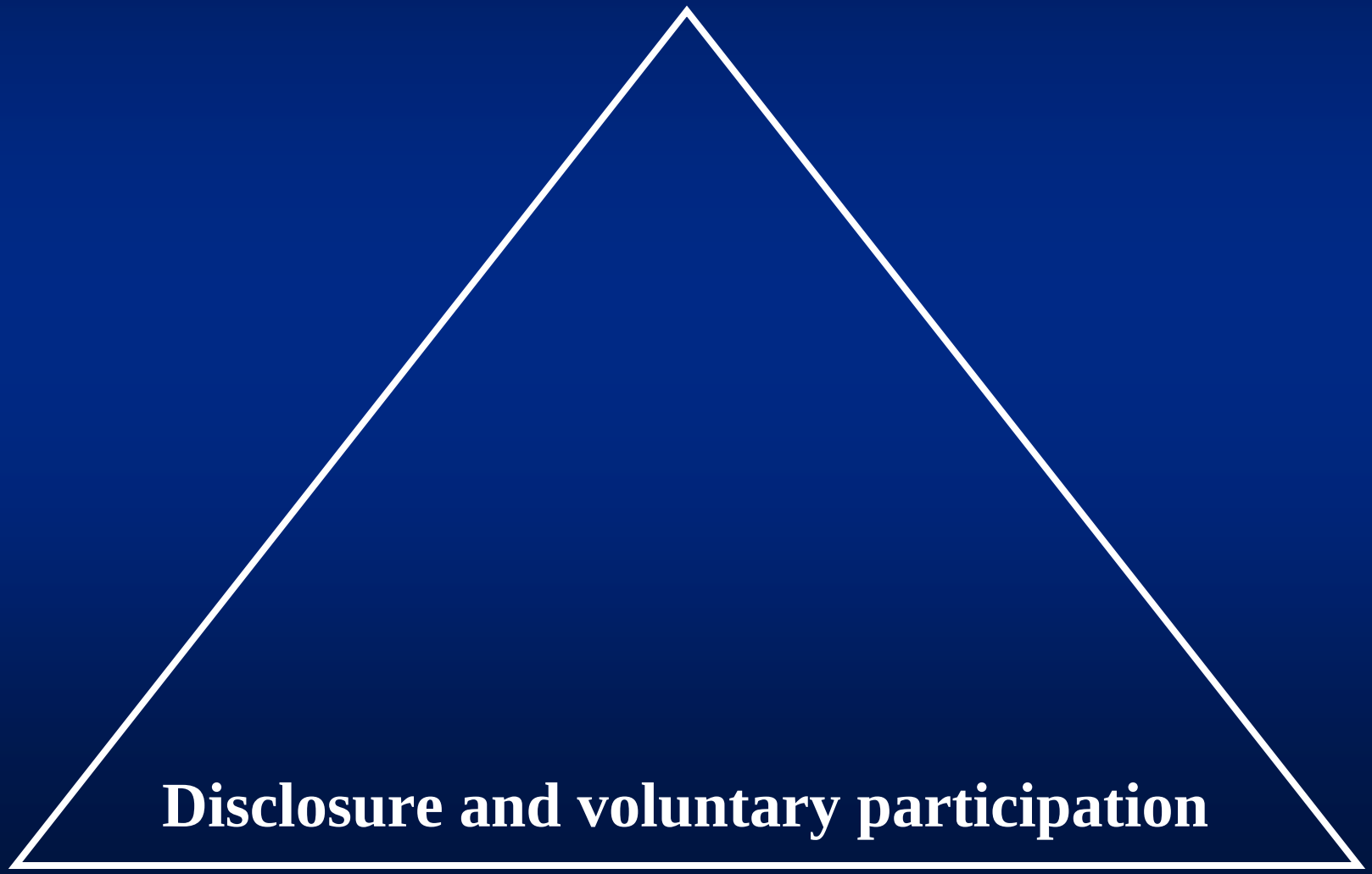
REASONING

if you decline, what will you do instead?

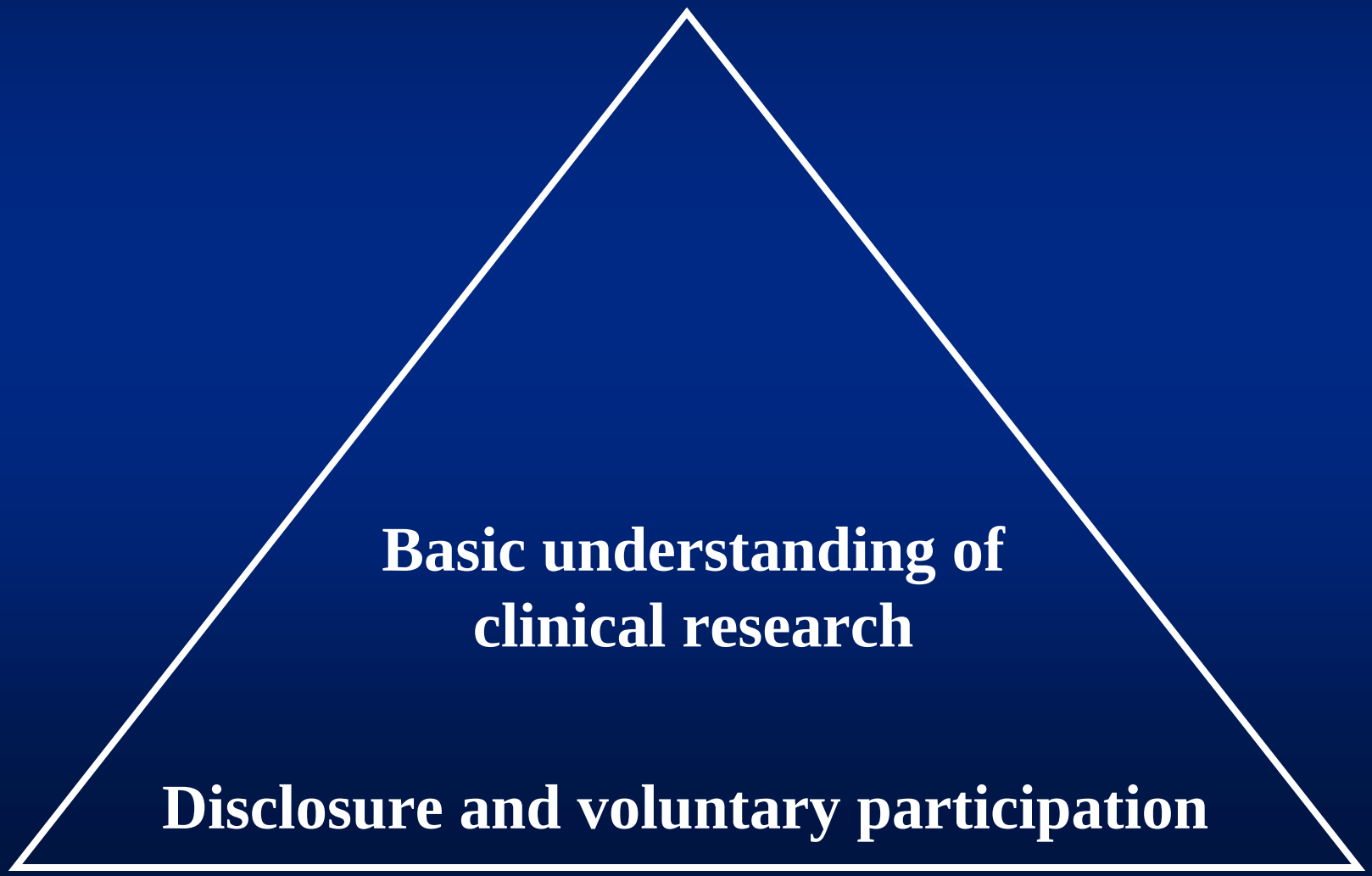
whose decision, can you stop participating?

CHOICE

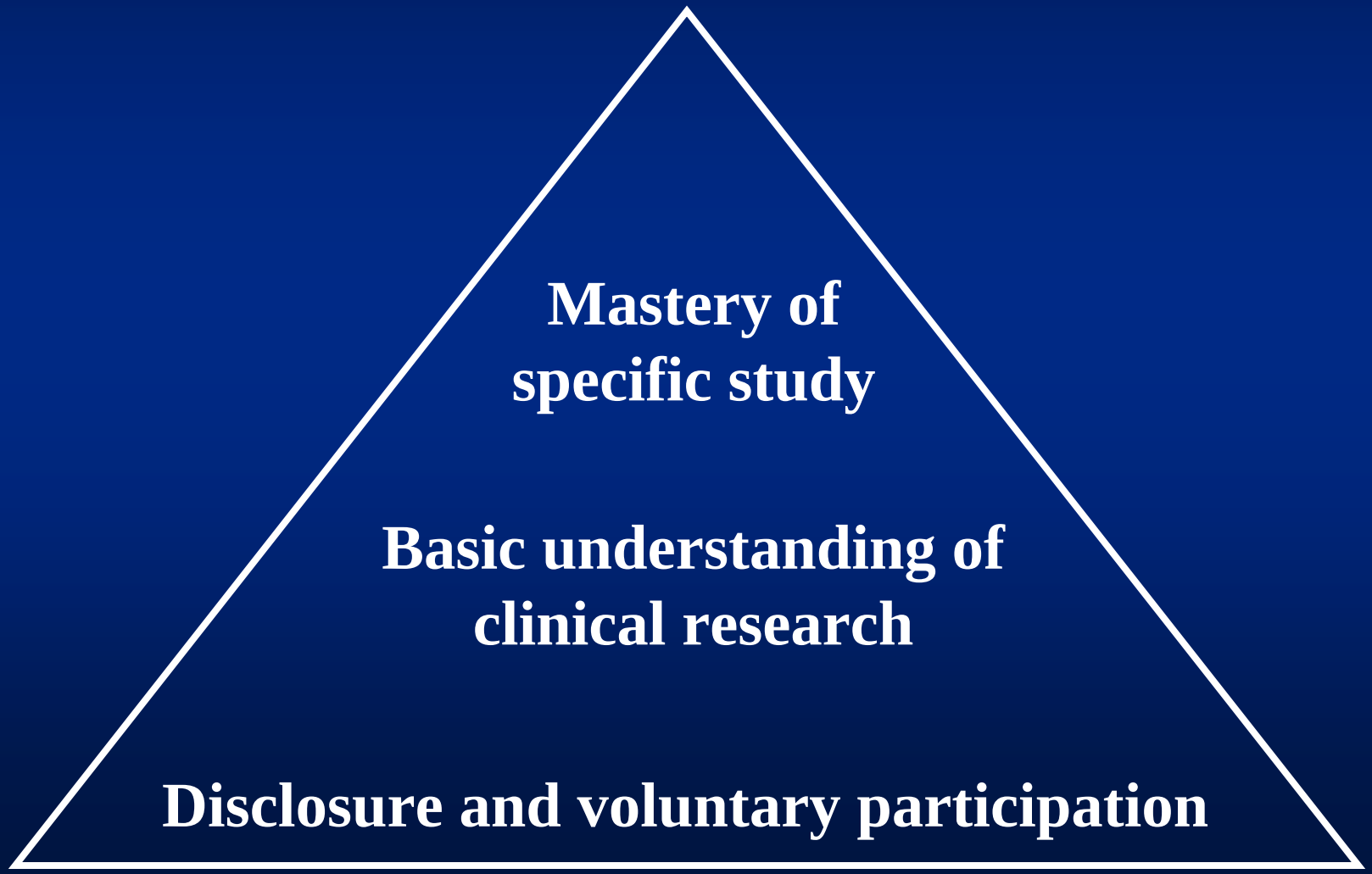
Consent Monitoring and Independent Capacity Assessment



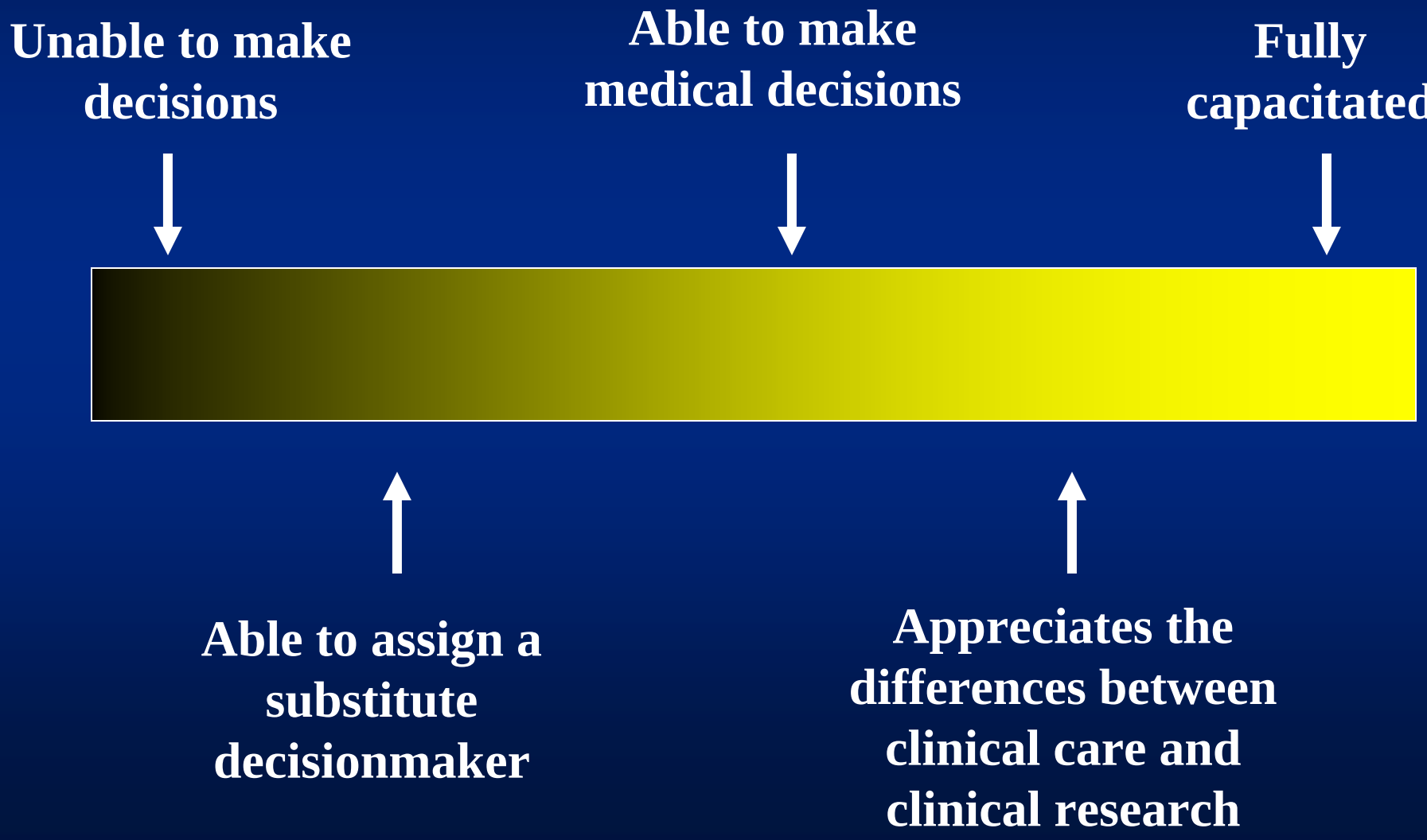
Consent Monitoring and Independent Capacity Assessment



Consent Monitoring and Independent Capacity Assessment



Decisionmaking Capacity



Conduct of Study

- Recruitment
- Capacity/consent assessment
- Research authorization
  - informed consent
  - surrogate authorization
- Monitoring
- Study termination

Additional Protections

- Clinical monitoring of ongoing research
- Data and safety monitoring boards
- Ethics consultation
- Informed consent monitoring
- Independent capacity assessment
- Advance directives and legally authorized representatives (e.g., guardianship, DPA)

NIH Advance Directive for Health Care and Medical Research Participation

I. Durable Power of Attorney

II. Advance Directive for Health Care

III. Advance Directive for Research Participation

NIH Advance Directive for Health Care and Medical Research Participation

- If I lose the ability to make my own decisions, I do not want to participate in any medical research.
- If I lose…I am willing to participate in medical research that might help me.
- If…won't help me but might help others as long as it involves no more than minimal risk of harm to me.
- If…that won't help me but might help others even if it involves greater than minimal risk of harm to me.

Data Analysis, Publication and Research Feedback to Participants

- Details of methods
- Disclosure of COI
- information-sharing with subjects
  - individual findings
  - aggregate data

Summary and Recommendations

- Is it necessary to enroll vulnerable subjects?
- Decisional capacity with respect to providing informed consent for a specific study
- Subject vulnerability, research risks and benefits:
  - Determined by local IRB
  - Defined by study population and specific protocol rather than by diagnosis alone

Summary and Recommendations (Cont.)

- Investigators should describe in detail:
  - methods of assessing decisional capacity
  - procedures for informed consent or proxy consent
  - provision of adequate safeguards
- IRBs should promote increased use of:
  - independent capacity assessment
  - consent monitors
  - legally authorized representatives
  - research advance directives
- IRB discretion regarding intermediate risk